The paradoxical effect of bevacizumab in the therapy of malignant gliomas

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ABSTRACT

One rationale behind the use of agents that inhibit vascular endothelial growth factor in the therapy of primary CNS malignancies is based upon the concept that normalization of tumor vasculature with a decrease in tumor interstitial pressure will improve access of cytoreductive drugs and improve radiotherapy efficacy due to increased oxygen delivery. However, several studies have raised the concern that these agents may both rapidly restore the low permeability characteristics of the blood–brain barrier and counteract the beneficial effect of pseudoprogression. The result may be decreased therapeutic efficacy while increasing infiltration by co-opting normal vessels. In this discussion, we examine both histologic and radiographic tumor progression in the context of antiangiogenic agents. Issues dealing with the safety of bevacizumab (Avastin®, Genentech, South San Francisco, CA) and its potential to decrease efficacy of standard radiochemotherapy when used to treat patients with newly diagnosed malignant glioma are emphasized.
Neurology® 2011;76:87–93

GLOSSARY

BBB = blood–brain barrier; **DCE** = dynamic contrast enhancement; **DSC** = dynamic susceptibility contrast; **FDA** = Food and Drug Administration; **FLAIR** = fluid-attenuated inversion recovery; **GBCA** = gadolinium-based contrast agent; **GBM** = glioblastoma multiforme; **IgG** = immunoglobulin G; **OS** = overall survival; **PFS** = progression-free survival; **RANO** = Response Assessment in Neuro-Oncology Working Group; **rCBV** = relative cerebral blood volume; **RTOG** = Radiation Oncology Therapy Group; **VEGF** = vascular endothelial growth factor.

Bevacizumab is a recombinant humanized monoclonal immunoglobulin G (IgG)1 antibody that binds to vascular endothelial growth factor (VEGF) and prevents the proliferation of endothelial cells and formation of new blood vessels.[1] VEGF has a role in endothelial cell survival, proliferation, invasion, and migration, which all affect tumor progression and angiogenesis.[2] Treatment with bevacizumab was quickly implemented for salvage therapy in progressive malignant gliomas after its efficacy was demonstrated in metastatic colon cancer[3] and in non-small-cell lung cancer.[4] Multiple groups using bevacizumab plus chemotherapy[2,5-12] and 2 phase II trials using bevacizumab alone[13,14] have demonstrated impressive imaging responses with increased overall survival (OS) and progression-free survival (PFS) in recurrent glioma patients relative to historical data in patients who received chemotherapy alone.[15,16] The results of the phase II trials were so compelling that in May 2009, the US Food and Drug Administration granted approval for the use of bevacizumab for the second-line treatment of glioblastoma multiforme (GBM).[17] Additionally, 2 recent phase II trials explored the use of bevacizumab plus chemotherapy as initial therapy for newly diagnosed GBM[18,19] and several other centers are enrolling patients in 2 large phase III trials of temozolomide and radiation with and without bevacizumab for the treatment of newly diagnosed GBM.[20,21]

VESSEL NORMALIZATION The general rationale behind using bevacizumab in combination with chemotherapy for malignant gliomas is twofold. First, bevacizumab normalizes vessels in the CNS by a mechanism similar to that of solid tumors outside the CNS. Bevacizumab decreases the abnormal morphology and organization of tumor-related vasculature that causes inefficient transport of oxygen and therapeutic drugs to

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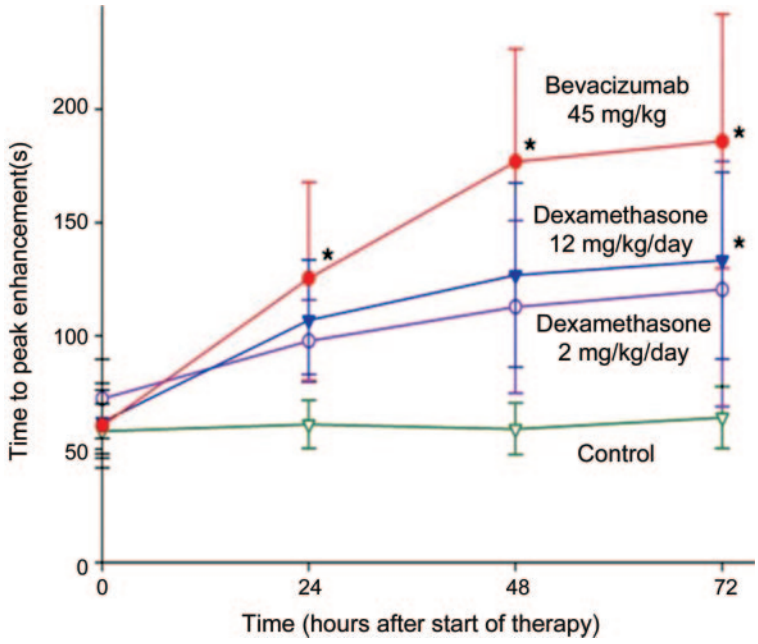
Disclosure: Author disclosures are provided at the end of the article.

the tumor.[22] As malignant glioma cells are known to express VEGF,[23] bevacizumab may have direct antitumor activity[24] and may increase tumor cell responsiveness to the cytotoxic effects of chemotherapy that penetrates into the tumor. Secondly, bevacizumab decreases tumor interstitial pressure, which is thought to improve delivery of chemotherapy to the tumor cells.[25]

In preclinical studies, bevacizumab has been shown to improve the delivery and efficacy of systemic chemotherapeutic agents in a neuroblastoma xenograft model.[26] However, extrapolating the mechanism of bevacizumab in non-CNS solid tumors to the mechanism of bevacizumab in malignant gliomas neglects the complexities of the blood–brain barrier (BBB) compared to the vasculature of solid tumors. Using another anti-VEGF agent, vandetanib, in a malignant glioma model, Claes et al.[27] demonstrated that the amount of apoptosis conferred by temozolomide (Temodar®, Schering-Plough, Kenilworth, NJ) was significantly decreased in animals that received vandetanib (Zactima™, AstraZeneca, London, UK). This led the authors to conclude that "Vessel normalization has an antagonizing rather than a synergistic or additive effect."[27] Vandetanib is a tyrosine kinase inhibitor with specificity toward epidermal growth factor receptor and VEGF receptor 2,[28] while bevacizumab blocks signaling through VEGF receptor 1 as well as VEGF receptor 2.[1] Given the similarities in the mechanisms of vandetanib and bevacizumab, the Claes et al. results potentially contradict the hypothesis that therapy targeting the VEGF pathway improves chemotherapy delivery to CNS tumors. In addition, the tumor phenotype changes in response to vessel normalization following treatment with bevacizumab, which may cause increased invasiveness and further resistance to antiangiogenic agents.[29] Using microdialysis techniques, Portnow et al.[30] demonstrated that the average maximum concentration of temozolomide in the brain compared to plasma was 13.6% lower than predicted by animal models. Future studies using similar microdialysis techniques with and without bevacizumab would more definitively elucidate the potential for bevacizumab to lower tumor temozolomide concentrations.

Figure 1 Time course for change in time to peak tumor enhancement



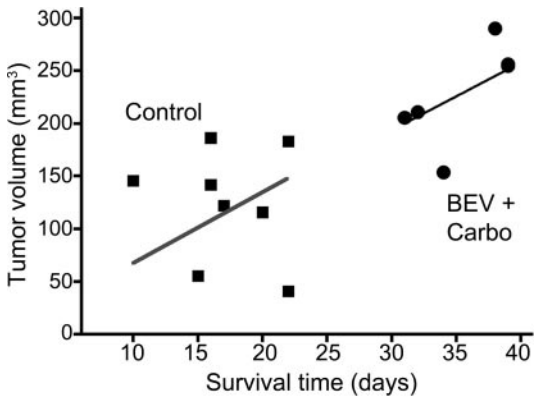
Serial dynamic contrast enhancement MRI at 12 T using gadodiamide was performed in rats with intracerebral U87 human glioma that were treated with bevacizumab or dexamethasone. Stars indicate significant increase in time to peak enhancement. (From Varallyay et al.[38] Figure reprinted with permission.)

PATTERNS OF TUMOR INVASION There is histologic evidence that tumors may adapt to antiangiogenic agents with increased tumor invasiveness and vessel cooption. In patients, de Groot et al.[31] recently identified "normalized" vessels adjacent to necrotic areas in GBM histologic specimens with tumor progression and necrosis occurring simultaneously with normalization and vessel pruning after treatment with bevacizumab. These findings were also seen in a malignant glioma model in which rats treated with bevacizumab had increased tumor with more invasive borders than controls.[31]

Patterns of tumor progression on MRI of patients receiving bevacizumab plus chemotherapy have also raised questions regarding tumor invasiveness. Zuniga et al.[32] found that 19 of 38 patients had both local and distant recurrence while another 4 had only distant progression, suggesting that inhibiting angiogenesis may result in normal vessel cooption and infiltration. This same study also showed progression on fluid-attenuated inversion recovery (FLAIR) MRI in 21 patients. Other groups have also observed significant distal progression and progression of nonenhancing tumor on FLAIR MRI.[33] The importance of FLAIR is increasingly being recognized in response assessment in the context of widespread antiangiogenic use by such groups as the Response Assessment in Neuro-Oncology Working Group (RANO)[34] and has been shown to be a more accurate biomarker of true tumor volume than postcontrast T1-weighted MRI.[35] Nonenhancing tumor progression has also been shown to be a negative prognostic factor independent of performance status.[33]

EFFECT OF ANTIANGIOGENESIS ON IMAGING Bevacizumab substantially decreases contrast enhancement on T1-weighted MRI in recurrent GBM

Figure 2 **Comparison of survival and tumor volumetrics**

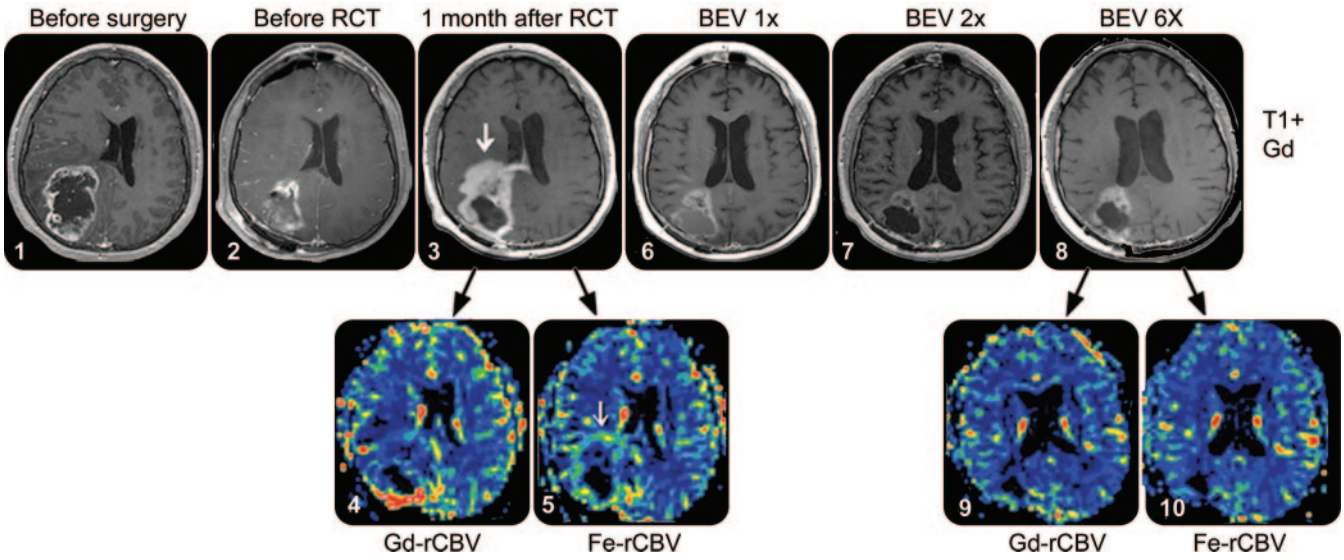


The survival time of rats with UW28 human glioblastoma intracerebral xenografts (days after tumor implantation) and the histologic tumor volumes (mm^3) are shown for each rat in the untreated control group (squares) and the bevacizumab (BEV) plus carboplatin (Carbo) treatment group (circles). The line indicates the linear regression for each group. (From Jahnke et al.[43] Figure reprinted with permission.)

and in preclinical malignant glioma models.[2,5-8,11,12,15,36-38] Using dynamic contrast enhancement (DCE) MRI at 12 T to compare the effects of bevacizumab vs high-dose dexamethasone on rat brain tumor vasculature, it was found that both dexamethasone and bevacizumab increased the time to peak enhancement compared to controls, a measure of gadolinium-based contrast agent leakage into tumor.[38] However, time to peak enhancement was significantly longer when animals received bevacizumab compared to high-dose dexamethasone (figure 1).[38] This suggests that the BBB stabilizing mechanisms of bevacizumab may be more profound than steroids. The molecular weight of the contrast agent used in that study, gadodiamide (Omniscan®, GE Healthcare, Mississauga, ON), is 574 g/mol,[39] and is similar to that of SN-38 (392 g/mol),[40] the active metabolite of irinotecan, the chemotherapeutic agent most frequently used in combination with bevacizumab to treat progressive malignant glioma. It stands to reason that if bevacizumab significantly decreases the permeability of gadodiamide, it may do the same for irinotecan. Using dynamic susceptibility contrast (DSC) MRI at 12 T to calculate relative cerebral blood volume (rCBV) in the same malignant glioma model, a significant reduction in rCBV was demonstrated when animals were treated with bevacizumab compared to dexamethasone or controls.[38,41] By decreasing both tumor permeability and blood volume, the mass effect of the tumor is decreased by bevacizumab even though there may be minimal or no actual antitumor effect.

CLINICAL RESPONSE The phase II study by Friedman et al.[13] showed that both irinotecan plus bevacizumab and bevacizumab alone conferred impressive OS in patients with progressive GBM in the context of previous studies before the use of bevacizumab.[15,16] The study was not powered to compare the 2 regimens head to head, so it is unclear if the addition of irinotecan to bevacizumab really confers a PFS or OS benefit. Long-term follow-up from this

Figure 3 **Bevacizumab decreases enhancement of pseudoprogression**

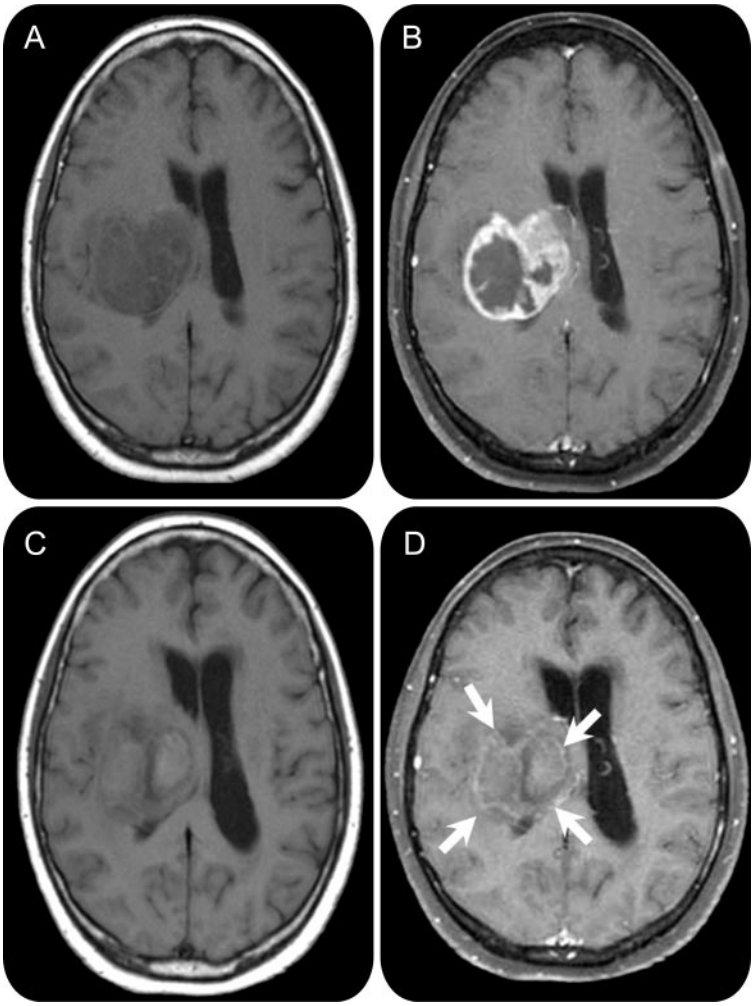


The top row shows serial postcontrast T1-weighted MRIs using gadoteridol (T1+Gd). Dynamic susceptibility contrast with Gd or ferumoxytol (Fe) were performed before and after radiochemotherapy (RCT) and bevacizumab (BEV). Red and orange indicate increased relative cerebral blood volume (rCBV). Bevacizumab decreases T1+Gd enhancement and rCBV of both true progression and pseudoprogression. (From Weinstein et al.[41] Figure reprinted with permission.)

study demonstrated a 4-year OS of 11%.[42] In contrast, a malignant glioma rat model demonstrated that the combination of bevacizumab plus carboplatin increased survival compared to either agent alone.[43] This begs the question: Do some chemotherapeutic agents have a potentially synergistic effect with bevacizumab while others do not? Interestingly, all animals treated with bevacizumab in that study lived longer but with increased tumor volume (figure 2).[43] It is conceivable that a major component of bevacizumab's efficacy is its ability to decrease tumor-related edema and blood volume thereby allowing patients to live longer with larger tumor volumes.

One potentially important confounding issue with bevacizumab is the effect on inflammatory and radiochemotherapy-induced changes in GBM vasculature. The term "pseudoprogression" is used to describe the phenomenon of subacute radiochemotherapy treatment–related sequelae in CNS tumors presenting as increasing lesion volume or new contrast enhancement on MRI suggestive of tumor progression. However, these patients often recover or stabilize spontaneously, usually without any change in treatment paradigm (figure 3).[44] The etiology of pseudoprogression is thought to be due to vascular and oligodendroglial cell injury, leading to inflammation and increased BBB permeability. Because the enhancement seen in pseudoprogression can be mistaken for actual tumor progression, patients are often routed to bevacizumab as second-line therapy for recurrence. Bevacizumab has been observed to decrease the permeability of not only tumor-related leaky vasculature but also of radiation-induced leaky vasculature, thereby "curing" biopsy-proven pseudoprogression.[41] This is particularly worrisome as pseudoprogression has been shown to be significantly associated with methylated *MGMT* promoter status and increased survival.[45] The presence of a methylated *MGMT* promoter is associated with a significant survival benefit.[45,46] The MGMT protein removes alkyl groups from the O^6 position of guanine. Silencing of the *MGMT* promoter by methylation is clinically important because cancer cells produce less MGMT protein and cannot repair DNA alkylation by agents such as temozolomide.[46] Bevacizumab may decrease the correlation between *MGMT* status and pseudoprogression.[45]

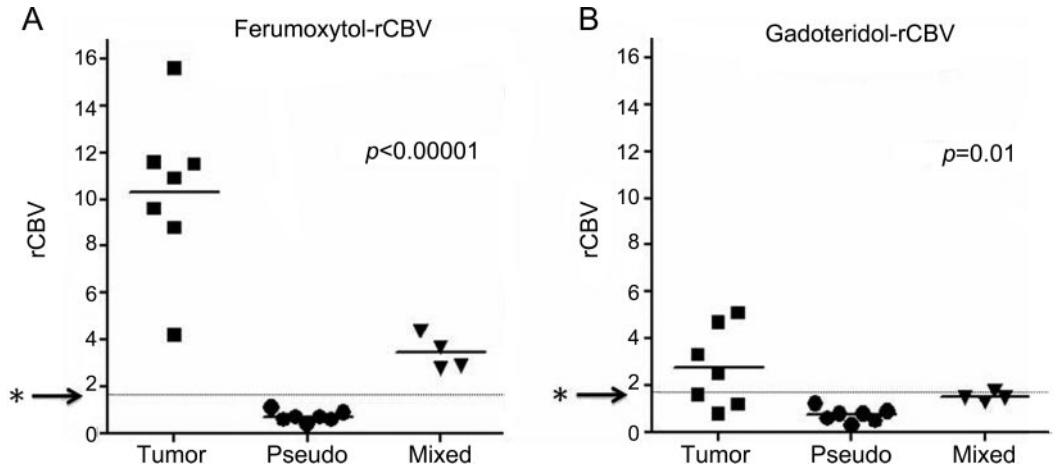
Figure 4 **Bevacizumab decreases enhancement when given up-front for glioblastoma multiforme (GBM)**



This patient received bevacizumab before standard radiochemotherapy for newly diagnosed GBM secondary to significant tumor volume increase and neurologic decline. (A) T1-weighted MRI before bevacizumab therapy. (B) Postcontrast T1-weighted MRI before bevacizumab therapy. (C) T1-weighted MRI 3 months after bevacizumab therapy. (D) Postcontrast T1-weighted MRI 3 months after bevacizumab therapy. Note the substantial decrease in tumor enhancement with gadoteridol after bevacizumab therapy (arrows) without concurrent reduction in tumor volume, mass effect, or midline shift.

THE FUTURE OF BEVACIZUMAB IN UP-FRONT MALIGNANT GLIOMA THERAPY Approximately 30% of patients who receive bevacizumab for recurrent malignant gliomas experience grade 3 and 4 toxicities.[10-12] This is deemed tolerable in the setting of salvage therapy and spares most patients the undesirable side effects associated with chronic high-dose steroid use. However, the side effects of bevacizumab for the up-front treatment of GBM have not been thoroughly addressed. Standard temozolomide and conformal radiation is generally well-tolerated. In the classic work by Stupp et al.,[47] only 7% of patients experienced grade 3 or 4 hematologic toxicities, 3% had severe infections, 33% had moderate to severe fatigue, 5% had thromboembolic complications, and less than 1% died from intracerebral hemorrhage. Preliminary data on the use of up-front bevacizumab in 75 patients shows a higher rate of toxicities, including fatigue in 16%, pulmonary embolism in 5%, thrombocytopenia in 10%, diarrhea in 5%, and sepsis and grade 2 intracerebral hematoma in one patient each.[18] In a smaller study of 10 pa-

Figure 5 Comparison of relative cerebral blood volume (rCBV) tumor progression and pseudoprogression



rCBV was obtained using both ferumoxytol and gadoteridol-based contrast agent. rCBV of 1.75 is a threshold to differentiate high- and low-grade gliomas.[52] (A) Dynamic susceptibility contrast (DSC) MRI using ferumoxytol as a blood pool agent demonstrated rCBV >4.2 in the tumor progression group (Tumor) and rCBV <1.1 in the pseudoprogression (Pseudo) group. The mixed group indicates that ferumoxytol-rCBV was high but gadoteridol-rCBV was inconsistent. (B) DSC MRI using gadoteridol demonstrated rCBV <1.7 in the 3 patients in the tumor progression group and rCBV <1.2 in the pseudoprogression group. A one-way analysis of variance was performed to evaluate the difference in rCBV values between active tumor, pseudoprogression, and mixed response groups. The difference was highly statistically significant for ferumoxytol ($p < 0.00001$) and significant for gadoteridol ($p = 0.01$). (From Gahramanov et al.[48] Figure reprinted with permission.) These findings suggest that ferumoxytol is a more reliable agent than gadoteridol to determine rCBV in high-grade gliomas.

tients also treated with up-front bevacizumab, 9 patients experienced grade 3 and 4 events during the postradiation phase.[19] Of particular concern, 2 patients in that study had wound breakdown.[19]

The Radiation Oncology Therapy Group (RTOG) is currently enrolling 720 patients with newly diagnosed GBM in a phase III randomized controlled trial to determine if adding bevacizumab during week 3 of standard radiochemotherapy improves PFS and OS.[20] The multinational AVAGLIO trial based in Europe is also a phase III trial with a similar design and plans to accrue 920 patients.[21] In the RTOG study, progression is evaluated using standard Macdonald criteria and does not incorporate the use of the nonenhancing tumor biomarkers FLAIR/T2 MRI as proposed by RANO.[34] Because bevacizumab decreases enhancement, PFS cannot be accurately measured by the Macdonald criteria (figure 4). Only select RTOG centers will use DCE and DSC MRI to evaluate tumor perfusion and permeability.[20] Future studies will likely increasingly incorporate dynamic MRI using not only gadolinium-based contrast agents (GBCA), but also blood pool agents such as ferumoxytol, which has demonstrated promising results in the differentiation of progression from pseudoprogression[48] (figure 5).

The timing of bevacizumab administration in the RTOG 0825 study is also concerning. In 2005, Cao et al.[49] showed that in nonenhancing tumor regions, the uptake of GBCA peaks between week 3 of radiochemotherapy and 1 month following the start of radiochemotherapy. This time period denotes the most significant BBB disruption and likely the most significant delivery of temozolomide. Thus, administering bevacizumab beginning week 3 of adjuvant radiochemotherapy will likely decrease this enhancement and potentially limit chemotherapy delivery during this therapeutic window. Although the mechanism of bevacizumab on the BBB in the CNS is not entirely clear, it is undoubtedly complex, and with an estimated monthly cost of $9,000[50] for 6 to 24 months, bevacizumab therapy is a serious economic issue. It should also be noted that despite the Food and Drug Administration (FDA)'s approval of bevacizumab for the treatment of recurrent GBM, not all governing medical bodies are convinced of its efficacy for this indication. The European counterpart of the FDA, the European Medicines Agency's Committee for Medicinal Products for Human Use, rejected the application to change the marketing authorization of bevacizumab to include recurrent GBM alone or in combination with irinotecan in November 2009.[51]

The purpose of this perspective is to raise issues that must be addressed prior to use of bevacizumab in newly diagnosed GBM. Clinical trials must be designed to specifically address the following questions: 1) Does adding chemotherapy to bevacizumab upfront improve outcomes compared to bevacizumab alone? 2) Does BBB stabilization by bevacizumab in-

crease chemotherapy delivery or actually decrease chemotherapy delivery to CNS tumors? 3) If bevacizumab has the potential to decrease chemotherapeutic delivery, would administering chemotherapy before bevacizumab help negate this effect? The timing of bevacizumab in relation to other therapeutic modalities (radiation and chemotherapy) will be highly dependent on the actual mechanism of bevacizumab in tumor vasculature. 4) What do we use to salvage our patients receiving up-front bevacizumab at recurrence? It is important to answer these questions when bevacizumab has the potential to paradoxically decrease temozolomide delivery and prevent pseudoprogression, both of which may affect survival.

DISCLOSURE

Dr. Thompson reports no disclosures. Dr. Frenkel serves as an Associate Editor for *Clinical and Applied Thrombosis/Hemostasis*; may accrue revenue on a patent re: Synergistic interaction of cyclic histone deactylase inhibitor with EGFR targeted drugs; and serves as a consultant for Shionogi & Co., Ltd. Dr. Neuwelt receives research support from the NIH and from the US Department of Veterans Affairs.

Received June 3, 2010. Accepted in final form August 24, 2010.

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